SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name

Bone grafting material containing a therapeutic biologic

Device Trade Name

GEM 21S™ (Growth Factor Enhanced Matrix)

Applicant's Name and Address

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Premarket Approval Application (PMA) Number

P040013

Date of Panel Recommendation

July 13, 2004

Date of Notice of Approval to Applicant November 18, 2005

II. Indications for Use

This device is indicated to treat the following periodontally related defects:

- Intrabony periodontal defects;
- Furcation periodontal defects; and,
- Gingival recession associated with periodontal defects.

III. Contraindications

As with any periodontal procedure where bone grafting material is used, *GEM 21S*™ is contraindicated in the presence of one or more of the following clinical situations:

(1) untreated acute infections at the surgical site;

(2) untreated malignant neoplasm(s) at the surgical site;

(3) patients with know ß-TCP or rhPDGF-BB hypersensitivity;

(4) intraoperative soft tissue coverage is required for a given surgical procedure but such coverage is not possible; and

(5) conditions in which general bone grafting is not advisable.

IV. Warnings and Precautions

The warnings and precautions can be found in the *GEM 21S™* labeling.

V. Device Description

GEM 21S™ is a combination of the following two individually marketed components:

(1) An osteoconductive, biocompatible and resorbable synthetic beta tri-calcium phosphate (β-TCP), that is a sterile, porous bone void filler used for the repair of bony defects. The β-TCP particle size used in the GEM 21S™ has been sieved to a particle size range of 250 to 1000 μm; and

(2) Becaplermin (rhPDGF-BB), a highly purified recombinant human platelet-derived growth factor.

GEM 21S™ is supplied in "kit" form with individual sterile components for single use and contains:

(1) a perio-cup of 0.5 cc of sterile β-TCP;

(2) a Hypak syringe containing a 0.5 ml of dilute (0.3 mg/ml) rhPDGF-BB sterile solution (Becaplermin) (in 20 mM NaAc Buffer) in identical volumetric proportion with β-TCP.

The kit is currently available in a single volume and a single concentration. The perio-cup containing the β-TCP may be stored at room temperature while the rhPDGF-BB should be stored under refrigeration and protected from light.

VI. Alternative Practices/Procedures

Other treatments for periodontal bone defects include autografts, allografts (implantation of bone from deceased individuals), implantation of synthetic bone materials (such as β-TCP, ceramics, and polylactic acid granules), and implantation of bovine-derived (cow) bone.

VII. Marketing History

GEM 21S™ has not yet been marketed. The two components comprising GEM 21S™, VitOss (β-TCP), and Regranex ("Becaplermin"), are each separately marketed. Consequently, the product marketing history presented below concerns these two individual components of GEM 21S™.

VitOss, for use as a bone void filler in orthopedic and periodontal applications, received marketing approvals in Australia (March 2001) and the European Union (October 2000). VitOss received marketing approval in United States (December 2000 and August 2003) for orthopedic applications, only. Regranex gel (Becaplermin), for use in the treatment of diabetic ulcers, received marketing approvals in the European Union (March 1999), Australia (August 1999), Canada (December 1998), and the United States (December 1997). VitOss and Regranex have not been withdrawn from these markets for any reasons. Furthermore, a review of FDA's Manufacturer and User Facility Device Experience Database (MAUDE), showed no records of adverse device experience with VitOss, confirming the continued safe use of this bone void filler.

VIII. Potential Adverse Effects of the Device on Health

Although no serious adverse reactions attributable to GEM 21S™ were reported in the 180 patient clinical trail, patients being treated with GEM 21S™ may experience any of the following adverse events that have been reported in the literature with regard to periodontal surgical grafting procedures: swelling, pain, bleeding, hematoma, dizziness, fainting, difficulty breathing, eating, or speaking, sinusitis, headaches, increased tooth mobility, superficial or deep wound infection; cellulites, wound dehiscence, neuralgia and loss of sensation locally and peripherally and anaphylaxis.

Occurrence of one or more of these conditions may require an additional surgical procedure and may also require removal of the grafting material.

IX. Summary of Nonclinical Studies

The nonclinical studies are summarized below:

Safety/Biocompatibility of GEM 21S™

Published data regarding the safety of GEM 21S™'s components and biocompatibility testing of the device are summarized below.

β-TCP

β-TCP is a purified, multicrystalline, porous form of calcium phosphate. The $Ca:PO_4$ ratio of β-TCP is 1:5 and is similar to that found in bone mineral (ref. 1-7). A number of animal and human studies have shown that β-TCP is compatible with host tissue and elicits no adverse reactions (ref. 2-16). Ingrowth of bone into the β-TCP bone substitute has been observed in numerous animal models for the treatment of various types of defects in numerous locations of the skeleton, as well as for human periodontal defects (ref. 17-26). In over 25 years of use as a bone void filler, there are no known reports in the literature of unfavorable responses to β-TCP. Additionally, there are no known interactions with drugs. The β-TCP used in GEM 21S has undergone biocompatibility testing in conformance with the ISO 10993 standard and has been determined to be biocompatible.

PDGF

Several published in vitro and in vivo studies containing data demonstrating that PDGF, when applied at the low, safe levels provided for in the GEM 21S™ device, has a beneficial effect on bone formation when used in a single application. Published studies show that PDGF is naturally present in the bone matrix and is produced locally at fracture sites (ref. 27-30) and is a necessary component in the promotion of normal fracture repair (ref. 31). PDGF has been shown to enhance bone repair when placed in a carrier in a bone defect (ref. 32,33,34). RhPDGF-BB has been shown to result in periodontal regeneration when placed with bone allograft (ref. 35).

In summary, there is an extensive body of scientific publications that support: (1) the role and effectiveness of PDGF in stimulating bone cell proliferation and recruitment; and (2) the acceptable safety profile of the single application PDGF contained in the GEM 21S™ as demonstrated by published clinical data on the safe use of PDGF at levels far exceeding the low levels of PDGF contained in GEM 21S™.

GEM 21S™

Tripartite biocompatibility testing in accordance with the standard EN ISO 10993-1:1997 "Biological evaluation of medical devices - Part 1: evaluation and testing" was conducted on the GEM 21S™ device. As previously noted, the individual components are marketed materials that individually has successfully undergone safety and biocompatibility testing. All studies on the GEM 21S™ device were performed in accordance with Good Laboratory Practice standards (GLPs). The following tests were performed.

- *In vitro* Genotoxicity: Bacterial Reverse Mutation (Ames) test with Salmonella and E. coli strains using saline and DMSO extracts. No evidence of mutagenicity to Salmonella and E. coli strains were observed.
- Sensitization in 15 Guinea Pigs using saline and cottonseed oil (CSO) extracts. Saline and cottonseed oil extracts from the device were individually injected intradermally into guinea pigs and occlusively patched. Following a recovery period, a challenge patch was placed. The sites were evaluated at 24 to 96 hours. No evidence of delayed dermal contact sensitization was observed for either extract.
- *In vitro* Cytotoxicity, MEM elution. An extract of β-TCP and Becaplermin (PDGF) was made using minimal essential medium, and flowed over a confluent monolayer of mouse fibroblasts. The confluency of the monolayer, percent lysis, and cellular characteristics were analyzed to determine potential cytotoxicity. The 1X MEM test extract showed mild or no evidence of causing mild cell lysis or toxicity. All samples exposed to the 1X MEM test extracts had a biological response of less than or equal to grade 2 (mild reactivity).
- Intracutaneous reactivity in rabbits that were intracutaneously injected with saline and cottonseed oil extracts from the device. As compared to blank vehicles as the control, there was no evidence of significant

irritation or toxicity from the extracts. There was evidence of slight irritation from the 0.9% sodium chloride USP solution injected intracutaneously into rabbits. The Primary Irritation Index Characterization for the cottonseed extract was negligible and slight for saline.

- Acute systemic toxicity in mice that were injected intravenously or intraperitoneally with saline and cottonseed oil extracts from the device. Under the conditions of this study, there was no mortality or evidence of systemic toxicity from the extracts.
- Muscle Implantation Study in the Rabbit. The test article was prepared and then was surgically implanted in muscle tissue of the rabbit. The muscle tissue was evaluated for evidence of irritation or toxicity. At 4 weeks, the macroscopic reaction was not significant as compared to the comparative control material and not significant as compared to the USP negative control implant material. Microscopically, the test article was classified as a non-irritant as compared to the comparative control material and a slight irritant as compared to the USP negative control article. Additionally, the comparative control was considered a slight irritant as compared to the USP negative control article.

The biocompatibility studies described above demonstrate the biocompatibility of GEM 21S™. There was no evidence of mutagenicity, delayed dermal contact sensitization, systemic toxicity and only slight to mild reactivity and irritation.

Furthermore, β-TCP has been used clinically for over 25 years with no published unfavorable adverse responses. Becaplermin gel (PDGF) (Regranex®), has been FDA approved for nearly eight years for at least 140 daily applications (20 weeks) to surgically excised wounds that extend into the subcutaneous tissue or beyond in the lower extremities of diabetics. Both components have a history of safe clinical use.

As noted previously, PDGF is a natural endogenous protein that lacks genotoxic potential. Additionally, it has a very low degree of absorption and a short half-life in plasma (36). When administered topically onto surgically excised wounds or subgingivally in periodontal defects, Becaplermin (PDGF) is quickly cleared [half-life of about four (4) hours] and has an insignificant effect on endogenous plasma PDGF concentrations (36, 37). For these reasons, Becaplermin is not considered to be a potential reproductive toxin or a systemic carcinogen. While no direct carcinogenicity or reproductive toxicity risk was identified, the device insert contains a precaution that carcinogenicity and reproductive toxicity studies for the GEM 21S™ device have not been conducted.

In summary, the extensive published data on the safety of VitOss and Becaplermin, FDA's clearance or approval of each of the individual components of GEM 21S™ (VitOss and Becaplermin) based, in part on the biocompatibility of these

products, and the ISO 10993 testing conducted by BioMimetic on the combination of these components demonstrate that GEM 21S™ is toxicologically safe and biocompatible.

PDGF Stability Studies and Packaging Testing

A comprehensive stability program of the GEM 21S™ biological component has been conducted for a period of 18 months following production. Shipping studies conducted on GEM 21S™ performed in accordance with recognized standards have demonstrated the acceptability of the GEM 21S™ kit under expected conditions of shipping and use.

Sterilization

The GEM 21S™ kit is not terminally sterilized after final assembly and packaging of the following three components, which are separately sterilized before kitting:

Filled β-TCP Perio-Cups

Filled β-TCP containers (perio-cups) are terminally sterilized by gamma irradiation. The sterilization cycle for the filled β-TCP perio-cups was validated in accordance with the requirements outlined in Method 1 of ISO Standard ISO 11137 for substantiation of a 25 kGy sterilization dose. The sterilization method produces a 10^{-6} or higher Sterility Assurance Level ("SAL"). The exterior of the cup is not sterile.

Sterile rhPDGF-BB

rhPDGF-BB is aseptically processed when manufactured. No terminal sterilization process is applied. The company employs a comprehensive environmental monitoring and control program to ensure the quality and integrity of the manufacturing process.

The aseptic filling of rhPDGF-BB into Hypak syringes is supported by the following validation packages:

- Sterile filtration validation; and,
- Media fill validation of aseptic filling process.

The aseptic fill validation studies followed standard Installation Qualification ("IQ"). Operational Qualification ("OQ"), and Process Qualification ("PQ") documentation. The exterior of the syringe is not sterile.

Microbiological Testing

Individual components of the GEM 21S™ kit underwent microbiological sterilization validation in accordance to their processing methods.

The β-TCP component is terminally sterilized by gamma irradiation and underwent a sterilization validation in accordance with the ISO 11137 standard which

demonstrated a sterilization assurance level (SAL) of 10^{-6}. In addition, the β-TCP component is placed on a formal stability program in accordance with ICH standards that assesses the sterility of the component annually.

The rhPDGF-BB component is aseptically processed in accordance with current GMPs for pharmaceutical products which included an aseptic fill validation. In addition, each lot undergoes sterility testing in accordance with USP methods. Finally, the rhPDGF-BB component is placed on a formal stability program in accordance with ICH standards that assesses the sterility of these components annually.

X. Summary Of Clinical Studies

The pivotal clinical study of GEM 21S™ is described in this section.

Introduction

A prospective, randomized double-blinded multi-center controlled clinical trial was performed in the United States to demonstrate the safety and effectiveness of GEM 21S™ in the management of periodontal defects and to assess the regenerative capability of GEM 21S™ on bone and soft tissue. As described in more detail below, this study compared results of treatment in three groups: low concentration, high concentration, and control. The effect of treatment on bone and soft tissue regeneration was assessed using Clinical Attachment Level ("CAL") and radiographic bone measurements. The duration of the study for each patient was almost six months (24 weeks).

The clinical study described in this section was performed pursuant to an approved Investigational Device Exemption ("IDE") Application, (G010340), which was conditionally approved on February 28, 2002 and approved without conditions on April 22, 2002. The IDE investigation was approved for 180 patients at 12 sites. The first patient was enrolled in the study on May 10, 2002 and the last patient visit was conducted on May 7, 2003.

Protocol Summary

The clinical study was carried out at 11 investigational sites in the United States. A total of 180 subjects were enrolled in the clinical trial, evenly divided between the three treatment groups. The three treatment groups were defined as follows:

Group I: GEM 21S™ with sodium acetate buffer containing 0.3 mg/mL rhPDGF-BB ("low concentration")

Group II: GEM 21S™ with sodium acetate buffer containing 1.0 mg/mL rhPDGF-BB ("high concentration")

Group III: β-TCP with sodium acetate buffer alone ("active control")

Eligibility Criteria

Subjects for this study were recruited from existing subject databases at each investigational site, referrals, and screening of volunteers responding to advertisements.

To be included in this study, subjects must have met all of the following criteria:

a. Aged 25-75,
b. No evidence of Localized Aggressive Periodontitis,
c. Treatment site with the following characteristics:
    - Probing pocket depth ≥7 mm at baseline,
    - After surgical debridement, ≥4 mm vertical bone defect with at least 1 bony wall,
    - Sufficient keratinized tissue to allow complete tissue coverage of defect, and
    - Radiographic base of defect ≥3 mm coronal to the apex of the tooth.
d. Give signed informed consent and be willing to comply with the follow-up visit schedule.

Subjects were excluded from the study if any of the following were true:

- Failure to maintain adequate oral hygiene during the lead-in phase,
- Woman pregnant or planning to become pregnant,
- History of oral cancer or HIV in the last 6 months,
- History of previous periodontal surgery on the study tooth within the last year,
- Study tooth exhibiting mobility of greater than Grade II,
- Study tooth exhibiting a Class III furcation defect,
- Clinical or radiographic signs of untreated acute infection at the surgical site, apical pathology, root fracture, severe root irregularities, cemental pearls, cemento-enamel projections not easily removed by odontoplasty, untreated carious lesions at the cemento-enamel junction (CEJ) or on the root surface, subgingival restorations and/or restorations with open margins at or below the CEJ,
- Weekly or more frequent use of smokeless chewing tobacco, pipe or cigar smoking, or smoking more than 20 cigarettes/day in the last 6 months,
- Allergy to yeast-derived products, or
- Using an investigational therapy within the past 30 days.

Study Visits

Patients in the study attended the following visits:

- Visit 1 (up to 6 months pre-surgery): Eligibility screening and informed consent
- Visit 2 (3 months pre-surgery): Scaling and root planning if necessary
- Visit 3 (2 months pre-surgery): Scaling and root planning if necessary
- Visit 4 (14 days pre-surgery): Baseline evaluation
- Visit 5: Periodontal surgery and device placement
- Visits 6-9 (post-surgical days 3-5, 6-9, 12-15, and 19-24): Wound healing assessment, pain assessment
- Visits 10-13 (post-surgical weeks 6, 12, 18 and 24): Clinical measurements and radiographs

Adverse events were ascertained at each post-operative visit and concomitant medications were recorded.

Primary Effectiveness Endpoint

The primary effectiveness endpoint for the study was a change in clinical attachment level (CAL) between baseline and 6 months. There were two hypotheses for this endpoint, to be evaluated sequentially:

1. Clinically meaningful efficacy: The mean change in CAL between baseline and 6 months was compared to a historically established level of clinical efficacy (1.5 mm) using a one-sample t-test.

2. Comparative efficacy: The mean change in CAL between baseline *and* 6 months was compared between Group I (low concentration) and Group III (control) using a two-sample t-test and a one-sided p-value of 0.05.

Secondary Effectiveness

The secondary effectiveness endpoints for the study were as follows:

1. Comparison of linear bone growth (LBG) and percent of original bone defect filled with new bone (%BF) based on radiographic measurements (Groups I and II versus Group III).
2. Area under the curve (AUC) for change in CAL, incorporating baseline, 3 month and 6 month data (Groups I and II versus Group III).

3. Change in CAL between baseline and 6 months (Group II versus Group III).
4. Pocket depth reduction (PDR) change between baseline and 6 months (all groups).
5. Gingival recession (GR) change between baseline and 6 months (all groups).
6. Wound healing (WH) during the first three weeks post-operatively (all groups).

Safety

Safety was monitored throughout the clinical trial by recording information on all adverse events. Adverse events were classified by the investigators according to severity (mild, moderate, severe) and relation to device (not related, unlikely to be related, likely related, definitely related). The investigator also recorded information on the action taken as a result of the adverse event. To assist in adverse event identification, investigators reviewed radiographs for evidence of ankylosis, root resorption, or other abnormal changes to the bony architecture.

Population Characteristics

Subjects were enrolled at 11 investigational sites in the United States. One hundred ninety five (195) subjects were enrolled into the study, of which 180 were randomized. Of the 15 subjects that were not randomized, 4 were excluded during screening and 11 were excluded during surgery. The 180 eligible patients were randomized into 3 groups, as defined above; 60 into Group I, 61 into Group II, and 59 into Group III.

Of the 180 randomized subjects, 178 completed the study. One subject from Group II (02-03) was lost to follow-up after Visit 10 (Week 6). One subject from Group III (04-12) withdrew from the study after Visit 6 (Day 3-5), but agreed to return for the 6 month visit clinical examination. Thus, 6 month outcomes are available for 179 subjects. No subjects were withdrawn from the study for non-compliance and no subjects withdrew from the study due to adverse events.

Baseline characteristics by treatment group can be found in **Table 10-1.** As shown in this table, there are no statistically significant differences between the treatment groups with respect to baseline characteristics.

Table 10-1: Baseline Characteristics by Treatment Group

	Group I (N=60) N (%)	**Group II (N=61) N (%)**	**Group III (N=59) n (%)**	**p-value**
Gender=Male	29 (48)	41 (67)	38 (64)	0.07
Race=Caucasian	33 (55)	37 (61)	37 (63)	0.39
Age (years) Mean±SD	49.4±10.2	50.4±13.0	52.8±9.5	0.22
Current Smoker	12 (20)	19 (31)	12 (20)	0.26

	Group I (N=60) N (%)	Group II (N=61) N (%)	Group III (N=59) n (%)	p-value
General Medical Abnormality	39 (65)	42 (69)	49 (83)	0.07
Dental Abnormality	16 (27)	11 (18)	15 (25)	0.48
CAL (mm) Mean±SD	9.1±1.8	8.8±1.6	8.8±1.5	0.50
PD (mm) Mean±SD	8.6±1.3	8.2±1.3	8.3±1.2	0.17
1-2 Wall Defect	46 (76)	49 (80)	45 (76)	0.30
Multi-rooted Defect	35 (58)	33 (54)	30 (51)	0.71
Vertical Bone Defect Depth (mm) Mean±SD	6.0±1.6	5.7±1.4	5.7±1.4	0.36
Width of Osseous Defect (mm) Mean±SD	3.7±1.3	3.5±1.1	3.7±0.9	0.61
Base of Defect to Root Apex (mm) Mean±SD	6.5±2.5	7.0±2.7	7.7±2.8	0.04

Results & Analysis

The test results are summarized below. An analysis of those results is also provided below.

Procedural Outcome

Primary flap closure was achieved in 100% of Group I subjects, and 98% of Group II and III subjects.

Good or excellent containment of study medication in the lesion was achieved in 92% of Group I subjects, 98% of Group II subjects, and 95% of Group III subjects. Good or excellent soft tissue closure was achieved in 100% of Group I and III subjects and 98% of Group II subjects.

Post-Procedure Outcomes

No days of work were missed due to the surgical procedure in 90% of Group I subjects, 92% of Group II subjects, and 98% of Group III subjects. Sutures were removed in less than 10 days in 20% of Group I subjects, 17% of Group II subjects, and 16% of Group III subjects. Good oral hygiene was maintained at all visits by 75% of subjects in each group.

Effectiveness

Table 10-2 summarizes the clinical outcome measurements (mean±SD CAL, PD, and GR) by treatment group and visit. These measurements are used to compute improvements from baseline, as presented in subsequent tables.

Table 10-2: Clinical Outcomes by Treatment Group and Visit

Outcome	Group I (N=60)	Group II (N=61)	Group III (N=59)
Clinical Attachment Level (CAL)			
Baseline	9.1±1.8	8.8±1.6	8.8±1.5
12 Weeks	5.4±1.6	5.5±1.5	5.5±1.7
24 Weeks	5.4±1.7	5.2±1.6	5.3±1.6
Pocket Depth (PD)			
Baseline	8.6±1.3	8.2±1.3	8.3±1.2
12 Weeks	4.4±1.3	4.1±1.1	4.1±1.1
24 Weeks	4.3±1.3	4.0±1.1	4.1±1.1
Gingival Recession (GR)			
Baseline	0.5±1.2	0.6±1.4	0.5±1.1
12 Weeks	1.0±1.4	1.4±1.4	1.4±1.2
24 Weeks	1.2±1.4	1.3±1.5	1.2±1.3

Primary Endpoint - CAL Gain

Clinically Meaningful Efficacy

Table 10-3 shows the mean CAL gain between baseline and 24 weeks for each treatment group. In addition, this table shows the 95% lower confidence bound for the mean and the one-sample t-test p-value comparing the mean with 1.5 mm, the historically established level of clinical effectiveness specified in the protocol.

Table 10-3: CAL Gain between Baseline and 24 Weeks by Treatment Group

CAL Gain	Group I (N=60)	Group II (N=60)	Group III (N=59)
Mean±SD (mm)	3.7±1.7	3.7±1.6	3.5±1.4
Median	4.0	3.5	3.0
Range (mm)	-2.0 to 7.0	-1.0 to 9.0	0.0 to 7.0
95% LCB	3.3	3.2	3.1
p-value	<0.001	<0.001	<0.001

As shown in **Table 10-3,** all three treatment groups had mean CAL gain well in excess of the established 1.5 mm level. Thus, the results for all treatment groups were considered to be clinically meaningful.

Comparative Efficacy

Table 10-4 shows the mean CAL gain between baseline and 12 weeks and between baseline and 24 weeks for Groups I and III. In addition this table shows the two-sample t-test p-value (one-sided) comparing Groups I and III at each time point.

Table 10-4: CAL Gain at Weeks 12 and 24 for Groups I and III

CAL Gain	Group I (N=60)	Group III (N=59)	p-value
Week 12			
Mean±SD (mm)	3.8±1.4	3.3±1.5	0.04
Median	3.0	3.0	-----
Range (mm)	1.0 to 8.0	-1.0 to 6.0	-----
Week 24			
Mean±SE (mm)	3.7±1.7	3.5±1.4	0.20
Median	4.0	3.0	-----
Range (mm)	-2.0 to 7.0	0.0 to 7.0	-----

As shown in **Table 10-4**, the difference in CAL gain at 12 weeks between Groups I and III (3.8 mm versus 3.3 mm) was statistically significant (p=0.04). Between Week 12 and Week 24 the CAL gain in Group I remained stable, while the CAL gain in Group III improved by 0.2 mm. Accordingly, the difference in CAL gain at Week 24 between Group I and Group III (3.7 mm versus 3.5 mm), while still numerically superior, is no longer statistically significant (p=0.20).

Secondary Endpoints – LBG and %BF

Of the 180 randomized subjects, 174 had data available for the radiographic analysis (60 in Group I, 58 in Group II, and 56 in Group III). **Table 10-5** shows the mean LBG and %BF between baseline and 24 weeks for each treatment group. In addition, this table shows the two-sample t-test p-value (one-sided) comparing Groups I and II with Group III, and the 95% lower confidence bound for the mean.

Table 10-5: LBG and %BF at 24 Weeks by Treatment Group

	Group I (N=60)	Group II (N=58)	Group III (N=56)
Linear Bone Growth (LBG)			
Mean±SD (mm)	2.52±1.96	1.53±1.61	0.89±1.71
Median (mm)	2.17	1.15	0.70
Range (mm)	-0.22 to 9.36	-1.80 to 6.97	-6.66 to 5.06
p-value	<0.001	0.02	-----
95% LCB	2.02	1.10	0.43
Percent Bone Fill			

	Group I (N=60)	Group II (N=58)	Group III (N=56)
(%BF)			
Mean±SE (%)	56.0±46.4	33.9±32.2	17.9±48.2
Median (mm)	49.5	33.0	19.7
Range (%)	-3.9 to 254.9	-22.8 to 108.1	-235.3 to 86.4
p-value	<0.001	0.02	-----
95% LCB	44.0	25.4	5.0

As shown in **Table 10-5**, for both LBG and %BF, Group I was superior to Group II and both were superior to Group III (Group I versus Group III: $p<0.001$; Group II versus Group III: $p=0.02$). For both LBG and %BF the mean for Group I was approximately three times the mean for Group III.

The literature-based thresholds for effectiveness were determined to be 0.5 mm for LBG and 15% for %BF. As shown in **Table 10-5**, the 95% lower confidence bounds substantially exceeded these thresholds for both Groups I and II. In contrast, the 95% lower confidence bounds for Group III (0.43 for LBG and 5% for %BF) do not exceed these thresholds.

Secondary Endpoint – Clinical and Radiographic Composite

To assess the cumulative beneficial effect for clinical and radiographic outcomes, two composite endpoints were defined with success criteria as follows:

1. CAL gain $\geq$ 2.7 mm and LBG $\geq$ 1.1 mm at 6 months
2. CAL gain $\geq$ 2.7 mm and %BF $\geq$ 14.1% at 6 months

These composite endpoints are presented in **Table 10-6**. In addition, this table shows the chi-square test p-value (one-sided) for the comparisons between Groups I and II and Group III.

Table 10-6: Composite Clinical and Radiographic Endpoints

	Group I N (%)	Group II N (%)	Group III N (%)
CAL+LBG	N=60	N=58	N=56
Composite Success	37 (62)	22 (38)	17 (30)
p-value	<0.0001	0.20	-----
CAL+%BF	N=60	N=60	N=59
Composite Success	(70)	(55)	(45)
p-value	0.003	0.13	-----

As shown in **Table 10-6**, 62% of subjects in Group I experienced success with respect to CAL gain and LBG, as compared to 38% for Group II and 30% for Group III. The difference between Group I and Group III was highly significant ($p<0.001$).

Likewise 70% of subjects in Group I experienced success with respect to CAL gain and %BF, as compared to 55% for Group II and 45% for Group III (p=0.003).

Secondary Endpoint – AUC for CAL Gain

In order to measure the cumulative results from the two time points (12 and 24 weeks), an Area Under the Curve (AUC) analysis was performed for CAL gain. This measurement is in units of "mm-weeks" (mm of CAL gain multiplied by number of weeks of follow-up). **Table 10-7** shows the CAL Gain AUC for all three treatment groups, as well as the two-sample t-test p-value (one-sided) for comparison of Groups I and II with Group III.

Table 10-7: CAL Gain AUC by Treatment Group

CAL Gain AUC	Group I (N=60)	Group II (N=60)	Group III (N=59)
Mean±SD (mm-weeks)	67.5±25.1	61.8±22.4	60.1±24.2
Median (mm-weeks)	63.0	59.6	58.2
Range (mm-weeks)	11.5 to 140	0.5 to 117	0.1 to 112
p-value	0.05	0.35	-----

As shown in **Table 10-7**, the CAL Gain AUC for Group I (67.5 mm-weeks) was significantly better than that for Group III (60.1 mm-weeks), with a p=0.05. This demonstrates that subjects in Group I maintained an overall level of improvement that was superior to that experienced by subjects in Group III. Referring back to the CAL gain values in **Table 10-3**, it is clear that, while both treatment groups ultimately achieved a similar degree of improvement, subjects in Group I improved more quickly than subjects in Group III.

Secondary Endpoint – CAL Gain Group II versus Group III

The primary effectiveness endpoint is a comparison of CAL gain at 24 months between Groups I and III. The comparison of CAL gain at 24 months between Groups II and III was made a secondary endpoint since it is only of interest if the low concentration product is effective and if there is a significant advantage to using the high concentration product instead of the low concentration. **Table 10-8** shows mean CAL gain at 24 weeks for Groups II and III, along with the two-sample t-test p-value (one-sided) for this comparison.

Table 10-8: CAL Gain between Baseline and 24 Weeks for Group II and Group III

CAL Gain	Group II (N=60)	Group III (N=59)
Mean±SE (mm)	3 7±0.2	3.5±0.2
Median (mm)	3.5	3.0
Range (mm)	-1.0 to 9.0	0.0 to 7.0
p-value	0.29	-----

As shown in **Table 10-8**, there is no significant difference in CAL gain at 24 weeks between Groups II and III (p=0.29).

Secondary Endpoints – GR and PDR

Tables 10-9A and 10-9B summarize the results for gingival recession (GR) and pocket depth reduction (PDR) at 12 and 24 weeks, respectively, for all three treatment groups. These tables also show the two-sample t-test p-values (two-sided) for the comparisons between Groups I and II and Group III.

Table 10-9A: GR and PDR at 12 Weeks by Treatment Group

	Group I (N=60)	Group II (N=60)	Group III (N=59)
Gingival Recession (GR)			
Mean±SD (mm)	0.5±1.0	0.7±1.0	0.9±1.2
Median (mm)	0.0	1.0	1.0
Range (mm)	-3.0 to 4.0	-1.0 to 3.0	-2.0 to 5.0
p-value	0.04	0.46	-----

	Group I (N=60)	Group II (N=60)	Group III (N=59)
Pocket Depth Reduction (PDR)			
Mean±SD (mm)	4.2±1.4	4.1±1.0	4.2±1.2
Median (mm)	4.0	4.0	4.0
Range (mm)	1.0 to 8.0	1.0 to 6.0	2.0 to 7.0
p-value	0.80	0.67	-----

Table 10-9B: GR and PDR at 24 Weeks by Treatment Group

	Group I (N=60)	Group II (N=60)	Group III (N=59)
GINGIVAL RECESSION (GR)			
Mean±SD (mm)	0.7±0.8	0.6±1.0	0.7±1.0
Median (mm)	0.5	0.0	0.0
Range (mm)	-1.0 to 3.0	-1.0 to 3.0	-2.0 to 3.0
p-value	0.95	0.81	-----
POCKET DEPTH REDUCTION (PDR)			
Mean±SD (mm)	4.4±0.2	4.3±0.2	4.2±0.2
Median (mm)	4.0	4.0	4.0
Range (mm)	1.0 to 7.0	2.0 to 9.0	1.0 to 9.0
p-value	0.38	0.66	-----

As shown in **Table 10-9B**, there were no significant differences between treatment groups with respect to GR and PDR at 24 weeks. As shown in **Table 10-9A**, consistent with the results for CAL gain, however, there was a statistically significant difference for GR at 12 weeks between Group I and Group III (0.5 mm versus 0.9 mm; p=0.04).

Secondary Endpoint – Wound Healing

A wound-healing scale modified from the index described by Lobene *et al.* (1986) was used to assess wound healing during the first three weeks post-surgery. This scale ranges from 0 (absence of inflammation) to 5 (severe inflammation).

Table 10-10 shows the wound healing scores for each of the 4 early post-surgical visits, for each treatment group. This table also shows the Cochran-Mantel-Haenszel p-value for comparison of Groups I and II with Group III.

Table 10-10: Wound Healing by Treatment Group

Wound Healing Score	Group I N (%)	Group II N (%)	Group III N (%)
Visit 6 (3-5 days)	**N = 60**	**N = 60**	**N = 56**
0	8 (13)	10 (17)	8 (14)
1	36 (60)	27 (45)	32 (57)
2	10 (17)	18 (30)	11 (20)
3	5 (8)	5 (8)	5 (9)
4	1 (2)	0 (0)	0 (0)
p-value	0.91	0.66	-----
Visit 7 (6-9 days)	**N = 59**	**N = 59**	**N = 58**
0	18 (30)	18 (30)	25 (43)
1	26 (44)	26 (44)	27 (47)
2	11 (19)	10 (17)	2 (3)
3	3 (5)	5 (8)	3 (5)
4	1 (2)	0 (0)	1 (2)
p-value	0.10	0.10	-----
Visit 8 (12-15 days)	**N = 60**	**N = 59**	**N = 58**
0	34 (57)	28 (48)	27 (47)
1	18(30)	19 (32)	22 (38)
2	2 (3)	11 (19)	7 (12)
3	5 (8)	1 (2)	2 (3)
4	1 (2)	0 (0)	0 (0)
p-value	0.81	0.89	-----
Visit 9 (19-24 days)	**N = 60**	**N = 60**	**N = 58**
0	43 (72)	36 (60)	32 (55)
1	12 (20)	19 (32)	19 (33)
2	3 (5)	2 (3)	3 (5)
3	1 (2)	3 (5)	3 (5)
4	1 (2)	0 (0)	1 (2)
p-value	0.14	0.44	-----

As shown in **Table 10-10**, by Visit 9 (approximately 3 weeks post-surgery), completing healing was experienced by 72% of subjects in Group I, 60% in Group II, and 55% in Group III. Although the Cochran-Mantel-Haenzsel test (which takes into account the ordinal nature of the wound healing score) p-value did not achieve statistical significance (p=0.14), a chi-square test contrasting complete healing (Grade 0) with incomplete healing (Grades 1-4), showed that the difference between Groups I and III was, indeed, statistically significant (p=0.03).

Safety

Adverse events (AEs) were collected throughout the study by patient inquiries during scheduled patient visits. **Table 10-12** summarizes the overall number and incidence of adverse events, as well as the number and incidence of severe AEs, serious AEs, and treatment related AEs.

Table 10-12: Summary of Adverse Events

Number of Events	Group I N=60	Group II N=61	Group III N=61	p-value
# Aes	88	93	89	-----
Number of Subjects	n (%)	n (%)	n (%)	-----
# Subjects with Aes	44 (73)	42 (69)	39 (66)	0.69
# Subjects with Severe Aes	0 (0)	2 (3)	2 (3)	0.47
# Subjects with SAEs	1 (2)	1 (2)	2 (3)	0.70
# Subjects with Related Aes	7 (12)	6 (10)	5 (8)	0.84

As shown in **Table 10-12**, 44 subjects (73%) in Group I experienced 88 adverse events (AEs), 42 subjects (69%) in Group II experienced 93 AEs, and 39 subjects (66%) in Group III experienced 89 AEs. Seven (7) subjects in Group I, six (6) subjects in Group II and five (5) subjects in Group III experienced AEs that were assessed by the investigator as likely or definitely related to the investigational product, none of which were considered serious. These 18 adverse events were all classified as surgical site reactions. Four (4) subjects experienced four (4) adverse events classified as "serious" (SAEs), none of which were directly attributable to the test product. The most frequently experienced AE for all treatment groups was pain at the surgical site, which was an expected sequelae following routine periodontal surgeries. There were no significant differences in the incidence of adverse events across the three treatment groups. There were no treatment-related serious adverse events and no subjects discontinued study participation due to adverse events.

Table 10-13 lists all AEs with incidence ≥2%, by treatment group and body system.

Table 10-13. Adverse Events by Body System and Treatment Group

Body System	Preferred Term	Group I N=60	Group II N=61	Group III N=59
BODY AS A WHOLE				
	Accidental injury	2 (3.3%)	2 (3.3%)	1 (1.7%)
	Allergic reaction	0 (0.0%)	1 (1.6%)	3 (5.1%)
	Back pain	5 (8.3%)	2 (3.3%)	1 (1.7%)
	Cyst	0 (0.0%)	2 (3.3%)	0 (0.0%)
	Flu syndrome	2 (3.3%)	3 (4.9%)	3 (5.1%)

Body System	Preferred Term	Group I N=60	Group II N=61	Group III N=59
	Headache	5 (8.3%)	3 (4 9%)	7 (11.9%)
	Malaise	0 (0.0%)	0 (0.0%)	2 (3 4%)
DIGESTIVE				
	Periodontal abscess	1 (1.7%)	1 (1.6%)	2 (3.4%)
	Stomach ulcer	0 (0.0%)	2 (3.3%)	0 (0.0%)
	Surgical site reaction	35 (58.3%)	35 (57 4%)	32 (54.2%)
	Tooth disorder	4 (6.7%)	7 (11.5%)	1 (1.7%)
	Tooth pain	3 (5.0%)	4 (6.6%)	4 (6.8%)
MUSCULOSKELETAL				
	Muscle pain	3 (5.0%)	1 (1.6%)	0 (0.0%)
RESPIRATORY				
	Respiratory disorder	2 (3.3%)	1 (1.6%)	3 (5.1%)
	Sinusitis	3 (5.0%)	0 (0.0%)	0 (0.0%)
SKIN/APPENDAGES				
	Herpes simplex	2 (3.3%)	0 (0.0%)	1 (1.7%)

As shown in **Table 10-13**, the most frequently experienced adverse event for all treatment groups was pain at the surgical site, which was an expected sequelae following the periodontal procedure employed for this trial. There were no differences in incidence of pain across the three treatment groups.

Multivariate Analysis

Subgroup analyses showed that increased LBG, improvement in %BF and higher CAL gains were observed in non-smokers compared to smokers, and subjects with three or circumferential apical bone walls compared with subjects with one or two apical bone walls. Improved effectiveness outcomes were seen in subjects with baseline areas of defect >21 mm^2, those who were ≤50 years of age, and non-Caucasians.

Additional analyses were performed to examine differences in CAL outcomes adjusting for demographic characteristics. In these analyses the following results were noted:

- No statistically significant differences were observed between treatment Groups I and III when comparisons were adjusted for age, gender, race and current smoking status ($p = 0.42$, ANCOVA model two-sided test).
- The study center by treatment interaction was found not to be statistically significant ($p = 0.12$, ANCOVA model two-sided test).
- No statistically significant differences were observed in the among-group comparison ($p = 0.70$, one-way ANOVA model).
- There was no observed linear concentration trend ($p = 0.41$, linear contrast ANOVA model).

Summary

Effectiveness

As shown in **Table 10-14**, below, Group I (β-TCP plus 0.3 mg/ml PDGF) achieved statistically beneficial results for gain in clinical attachment levels and less gingival recession at three (3) months as well as gain in linear bone growth and increased bone fill at six (6) months, compared to the active control Group III which received β-TCP alone. The clinical significance of these results is confirmed by comparison to historical benchmarks of effectiveness for other approved treatments. Furthermore, the beneficial effects of GEM 21S™ were observed in all types of defects, including one to three wall and circumferential defects. These results address an unmet clinical need in that GEM 21S™ provided a clear benefit even in the most severe cases where β-TCP alone was ineffective. Thus, GEM 21S™ provided a more predictable treatment option for all types of defects than the active β-TCP control.

Table 10-14. Summary of Clinical and Radiographic Effectiveness of GEM 21S™

Summary of GEM 21S™ Effectiveness				
Endpoint		**Group I**	**Group II**	**Group III**
CAL Gain (mm): 3 months		3.8 (p=0.04)	3.4 (p=0.40)	3.3
CAL: AUC Analysis (mm x wk)		67.5 (p=0.05)	61.8 (p=0.35)	60.1
CAL (mm): 95% LCB at 6 months		3 3	3.2	3 1
GR (mm): 3 months		0.5 (p=0.04)	0 7 (p=0.46)	0.9
LBG (mm): 6 months		2.5 (p<0.001)	1.5 (p=0.02)	0.9
%BF: 6 months		56.0 (p<0.001)	33.9 (p=0.02)	17.9
Composite Analyses (% Success)	CAL-LBG	61.7% (p<0.001)	37.9% (p=0.20)	30.4%
	CAL-%BF	70 0% (p=0.003)	55.2% (p=0.13)	44.6%

XI. Kappa-Analysis

The PMA also summarizes the results of the Kappa analysis regarding intra-examiner reproducibility and inter-examiner constancy of probing measurements, which FDA requested. The Kappa score was 0.9357 (p<0.0001) for intra-examiner reproducibility. The Kappa score was 0.8901 (p<0.0001) for inter-examiner consistency. Thus, the probing measurements were both reproducible within each investigator and consistent across investigators.

XII. Conclusions Drawn From the Studies

GEM 21S™ was shown to be safe and effective in the restoration of alveolar bone and clinical attachment around teeth with moderate to advanced periodontitis in a large, randomized clinical trial involving 180 subjects studied for up to 6 months.

Although the long term results of use of this device were similar to those of other bone filling devices without growth factors on the U.S. market, the three month data results indicated an improved clinical result, as demonstrated by an improved CAL measurement. The clinical implication is that this device may facilitate earlier resolution of periodontal intrabony lesions.

XIII. Panel Recommendation

At an advisory meeting held on July 13, 2004, the Dental Products Panel recommended that Biomimetics Pharmaceuticals' PMA for GEM 21S™ be approved subject to the following conditions:

- There should be no labeling claims of superiority over other devices considering the primary endpoint and
- Labeling should be restricted to use only for periodontal-related defects.

XIV. CDRH Decision

FDA concurred with the panel recommendation and the labeling reflects the conditions.

The applicant has agreed to establish and validate an immunological identity test for rhPDGF received from the manufacturer. The information will be submitted as a supplement for FDA review by June 1, 2006. Following review and approval by the FDA, the new assay will replace SDS-PAGE as an identity test for incoming bulk drug substance.

The company has also agreed to evaluate the historical release and stability specifications for GEM21S following manufacture of 30 lots of product and submit the results to FDA with any proposed changes by September 1, 2006. Any proposal to broaden or shift the specifications should be submitted as a supplement to the premarket approval application. If there is no change in specifications submit this information with the annual report.

The company has agreed not to use lots of PDGF drug substance for manufacture of GEM21S which was fermented after September 2002 until supplemental approval is received from FDA to include the PDGF fermentation site.

The fermentation site was withdrawn from consideration in this PMA. All remaining manufacturing facilities were inspected and found to be in compliance with the Quality System Regulations (21 CFR 820).

CDRH issued an approval order on November 18, 2005.

XV. Approval Specifications

Directions for Use: See labeling.

Hazards to health from use of the device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval requirements and restrictions: See approval order.

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